Heart rate variability in patients with idiopathic Parkinson's disease with and without obstructive sleep apnea syndrome

Valko, P O ; Hauser, S ; Werth, E ; Waldvogel, D ; Baumann, C R

Abstract: BACKGROUND: Obstructive sleep apnea syndrome (OSAS) is associated with repeated apnea-induced sympathetic surges leading to specific alterations of the power spectrum of heart rate variability (HRV). Sympathetic dysfunction evolves early in idiopathic Parkinson's disease (PD), but the consequences on cardiac autonomic response to OSAS have not been studied so far in PD patients. METHODS: Sixty-two patients with PD (35 without OSAS (PD-wo), 27 with OSAS (PD-OSAS)) and 62 age-matched control subjects (25 without OSAS (Co-wo), 37 with OSAS (Co-OSAS)) were included. HRV variables - including mean R-R interval, standard deviation of all normal-to-normal R-R intervals (SDNN), both low frequency (LF) and high frequency (HF) power bands, and the LF/HF ratio - were computed automatically from full-night polysomnography and calculated separately for each sleep stage. RESULTS: HRV variables were similar in PD-wo and PD-OSAS. In contrast, Co-OSAS showed significantly higher LF power in NREM1 and NREM2 sleep and higher LF/HF ratio in NREM1, NREM2 and slow wave sleep than Co-wo. Similarly, correlations between HRV variables and parameters of OSAS severity were found only in controls but not in PD patients. CONCLUSION: Our results suggest that the sympathetic response to OSAS is blunted in PD, giving further clinical evidence of the sympathetic denervation commonly observed in this neurodegenerative disorder.

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Corresponding Author: Dr. Philipp Oliver Valko, M.D.

Corresponding Author's Institution: University Hospital of Zurich

First Author: Philipp Oliver Valko, M.D.

Order of Authors: Philipp Oliver Valko, M.D.; Sabrina Hauser, M.Sc.; Esther Werth, Ph.D.; Daniel Waldvogel, M.D.; Christian R Baumann, M.D.

Abstract: Background: Obstructive sleep apnea syndrome (OSAS) is associated with repeated apnea-induced sympathetic surges leading to specific alterations of the power spectrum of heart rate variability (HRV). Sympathetic dysfunction evolves early in idiopathic Parkinson's disease (PD), but the consequences on cardiac autonomic response to OSAS have not been studied so far in PD patients.
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Conclusion: Our results suggest that the sympathetic response to OSAS is blunted in PD, giving further clinical evidence of the sympathetic denervation commonly observed in this neurodegenerative disorder.

Author Declaration

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1. Studies with human subjects must have been conducted in accordance with the Declaration of Helsinki. All persons must have provided informed consent prior to being included in the study.

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3. Protocols with animal or human subjects must have been approved by the relevant local committee(s) charged with ensuring subject protection. Studies that entail pain or distress will be assessed in terms of the balance between the distress inflicted and the likelihood of benefit.

4. The authors declare that the manuscript is original, that it is not being considered for publication elsewhere, and that it will not be submitted elsewhere while still under consideration for Parkinsonism & Related Disorders or after it has been accepted by Parkinsonism & Related Disorders.

5. All authors have seen and approved the manuscript in the form submitted to the journal. The authors declare that they have conformed to the highest standards of ethical conduct in the submission of accurate data and that they acknowledge the work of others when applicable.

6. All sources of financial support for the work have been declared in the Acknowledgements section of the manuscript. Any additional conflicts of interest must also be declared. Please include declarations of any consultancy or research funding received from relevant companies from three years prior to performance of the research until the time of manuscript submission. If the research is supported by internal funds, that should be stated as well.

To indicate compliance with the preceding declaration and that you have obtained agreement from all of the authors of this paper to declare their compliance as well, please place an x here: __x_

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*Cover Letter

Philipp O. Valko, MD
Department of Neurology
University Hospital of Zurich
Frauenklinikstrasse 26
CH – 8091 Zürich
Switzerland

Prof. R. F. Pfeiffer, MD
Editor of *Parkinsonism and Related Disorders*
University of Tennessee HSC
Department of Neurology
875 Monroe Avenue
Memphis TN 38163

Re: Heart rate variability in patients with idiopathic Parkinson's disease with and without obstructive sleep apnea syndrome

Dear Prof. Pfeiffer,

We would like to submit our manuscript entitled "Heart rate variability in patients with idiopathic Parkinson's disease with and without obstructive sleep apnea syndrome" for consideration as original full length article in *Parkinsonism and Related Disorders*.

The results of our study suggest that the characteristic sympathetic response to obstructive sleep apnea syndrome is blunted in patients with Parkinson's disease, which is most likely explained by the sympathetic denervation commonly observed in this neurodegenerative disorder. Since obstructive sleep apnea syndrome is a common comorbidity in Parkinson's disease – recent reports point to a prevalence of up to 45-60% - we believe that our findings might be of clinical relevance.

The article contains original material, which has not been previously published, and is not in consideration for publication in any other journals.

The manuscript was seen and approved by all authors in its final form. There are no financial disclosures, and the authors report no conflicts of interest.

Sincerely,

Philipp O. Valko, MD

Reply to the reviewers

Heart rate variability in patients with idiopathic Parkinson's disease with and without obstructive sleep apnea syndrome

Valko PO, Hauser S, Werth E, Waldvogel D, Baumann CR

Thank you very much for reconsidering our above-mentioned revised manuscript for publication in *Parkinsonism and Related Disorders*. A revised version has been written based on the comments of the reviewers (changes in the manuscript are highlighted in yellow).

Reviewer #1: ***The authors have retrospectively studied the data collected from PD patients with and without OSAS and compared these with age and gender matched controls with and without OSAS. The sympathetic drive seen in controls with OSAS was blunted in PD patients with OSAS suggesting early involvement of autonomic system in agreement with Braak's hypothesis.***

Apparently no changes required.

Reviewer #2: ***Increased sympathetic nerve activity has been observed in patients with obstructive sleep apnea syndrome (OSAS), and increased vascular morbidity in these patients is believed to be caused by this abnormal autonomic cardiovascular regulation. While the effect of OSAS on cardiac autonomic function is known to be altered in patients with neurological conditions affecting the autonomic nervous system, e.g. familial dysautonomia or pure autonomic failure, cardiac autonomic responses to OSAS has not been assessed yet in Parkinson's disease (PD).***
This is a retrospective study that aims to evaluate sympathetic autonomic response to OSAS, as measured by heart rate variability, in patients with PD compared with PD patients without OSAS and healthy controls with and without OSAS. The authors find that the sympathetic response to OSAS is blunted in PD, thus lacking the normal sympathetic response to OSAS. This finding gives further clinical evidence of the sympathetic denervation commonly observed in PD patients. As authors underline, the clinical implications and the prognostic significance of these observations might be that the autonomic deficiency might protect PD patients with OSAS from the typical cardiovascular consequences.
This study is interesting, innovative, well written and might have clinical and prognostic connotations. As authors highlight, limitations of this study are due to its retrospective design and drugs that can modify autonomic responses (e.g., dopaminergic treatment) were not withdrawn at the time of the HRV analysis. Further prospective studies to confirm these finding are warranted.
I have some specific comments:

Methods: I suggest replacing "standard deviation of all R-R intervals (SDNN)" with "standard deviation of all normal-to-normal RR intervals (SDNN)".
The wording has now been changed as suggested by the reviewer.

Results:
Authors should add data of the dopaminergic treatment (i.e., levodopa equivalent daily dose) of PD patients, perhaps in table 1.
A detailed overview on the patients' dopaminergic treatment is provided in Table 3 (supplementary file, will be printed in the online version).

Table 3

	PD-wo (n = 35)	PD-OSAS (n = 27)	*p*
Levodopa	15 (43%)	16 (59%)	NS
Only levodopa	10 (29%)	3 (11%)	NS
DA	19 (54%)	18 (67%)	NS
Nonergot DA	17 (49%)	16 (59%)	NS
Ergot DA	2 (6%)	4 (15%)	NS
Only DA	6 (17%)	2 (7%)	NS
Both levodopa + DA	13 (37%)	16 (59%)	NS
Levodopa + entacapone	8 (23%)	6 (22%)	NS
No dopaminergic drugs	8 (23%)	6 (22%)	NS
LDE, mg/d	490 ± 400	538 ± 457	NS

DA dopamine agonist LDE Levodopa Dosage Equivalent

Presence of autonomic disturbances has been detected only by history or clinical signs. Are there any data on tests assessing the autonomic nervous system function (e.g., cardiovascular reflex testing)?
Unfortunately, no ancillary autonomic tests such as the cardiovascular reflex testing have been performed in our patients. We agree that this represents a limitation of our study. We have added a specific comment on this in the corresponding paragraph of the discussion.

Please specify which kind of autonomic disturbances had these patients.
This is now specified in the Results section.

Thank you again for reconsidering our manuscript for publication.

With kind regards,

Philipp O. Valko

Boston, 25.11.2011

Revised version: 25.11.2011

For: Parkinsonism and Related Disorders

Heart rate variability in patients with idiopathic Parkinson's disease with and without obstructive sleep apnea syndrome

Philipp O. Valko[1*], MD
Sabrina Hauser[1*], MSc
Esther Werth[1], PhD
Daniel Waldvogel[1], MD
Christian R. Baumann[1], MD

Department of Neurology[1], University Hospital of Zurich, Switzerland

*The first 2 authors contributed equally to this study

Correspondence:

Philipp O. Valko, MD
Department of Neurology
University Hospital of Zurich
Frauenklinikstrasse 26
8091 Zurich, Switzerland
Tel. +41 44 255 55 11
Fax +41 44 255 43 80
E-mail: phvalko@gmx.ch

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Abstract

Background: Obstructive sleep apnea syndrome (OSAS) is associated with repeated apnea-induced sympathetic surges leading to specific alterations of the power spectrum of heart rate variability (HRV). Sympathetic dysfunction evolves early in idiopathic Parkinson's disease (PD), but the consequences on cardiac autonomic response to OSAS have not been studied so far in PD patients.

Methods: Sixty-two patients with PD (35 without OSAS (PD-wo), 27 with OSAS (PD-OSAS)) and 62 age-matched control subjects (25 without OSAS (Co-wo), 37 with OSAS (Co-OSAS)) were included. HRV variables – including mean R-R interval, standard deviation of all normal-to-normal R-R intervals (SDNN), both low frequency (LF) and high frequency (HF) power bands, and the LF/HF ratio – were computed automatically from full-night polysomnography and calculated separately for each sleep stage.

Results: HRV variables were similar in PD-wo and PD-OSAS. In contrast, Co-OSAS showed significantly higher LF power in NREM1 and NREM2 sleep and higher LF/HF ratio in NREM1, NREM2 and slow wave sleep than Co-wo. Similarly, correlations between HRV variables and parameters of OSAS severity were found only in controls but not in PD patients.

Conclusion: Our results suggest that the sympathetic response to OSAS is blunted in PD, giving further clinical evidence of the sympathetic denervation commonly observed in this neurodegenerative disorder.

Introduction

Increased vascular morbidity in patients with obstructive sleep apnea syndrome (OSAS) is believed to be caused by abnormal autonomic cardiovascular regulation [1]. In this line, obstructive sleep-related apnea events are characterized by progressive bradycardia during respiratory effort and abrupt tachycardia after reopening of the airways, which leads to cyclical variations of heart rate [2]. Studies using spectral analysis of heart rate variability (HRV) have shown that OSAS is accompanied by an increase of low frequency power bands, which is believed to reflect sympathetic activity [3]. Likewise, both increased sympathetic nerve activity and high levels of circulating norepinephrine during wakefulness have been observed in patients with OSAS [4-6]. During sleep, obstructive apneas are accompanied by transient vasoconstriction in the limbs, again suggesting apnea-induced sympathetic activation [7]. Finally, there is evidence that alteration of HRV and overactivity of the sympathetic nervous system is reversible during treatment with continuous positive airway pressure [6, 8].

The effects of OSAS on cardiac autonomic function may be altered in patients with neurological conditions affecting the autonomic nervous system (ANS). Earlier studies in patients with familial dysautonomia or pure autonomic failure reported that even severe apneas were not associated with the usual cardiac response, suggesting a decoupling of the heart rate from the respiratory cycle in neurodegenerative disease [9, 10].

In idiopathic Parkinson's disease (PD), there is growing evidence for sympathetic denervation of the heart. Neuroimaging studies using different sympathiconeural imaging agents demonstrated reduced sympathetic innervation of the heart in patients with PD [11, 12]. Considering the important pathophysiological involvement of the ANS in OSAS and its primary impairment in PD, it is surprising that the cardiac autonomic response to OSAS has not yet been studied in PD patients. Therefore, the primary goal of this study was to test the hypothesis whether the normal sympathetic response to OSAS is blunted in PD. In addition,

we aimed at identifying possible consequences of this sympathetic denervation in PD patients with OSAS.

Methods

This retrospective study was conducted at the Department of Neurology of the University Hospital of Zurich, Switzerland.

Subjects. We analyzed the data of 115 consecutive patients with idiopathic Parkinson's disease (PD). All patients were examined in our Movement Disorders outpatient clinic and in our sleep laboratory between January 2005 and June 2010. Fifty-three PD patients were diagnosed with OSAS (PD-OSAS), and 59 had no clinical or polysomnographic signs of OSAS (PD-wo). Three PD patients with apneas of mainly central origin were excluded.

As control groups, we included 80 consecutive patients, who have been diagnosed with OSAS (Co-OSAS), and 53 subjects without OSAS (Co-wo), i.e. without polysomnographic abnormalities. We excluded subjects with cardiovascular disease, cardiac arrhythmia, concomitant diabetes, neurological disorders, additional sleep-wake disorders such as narcolepsy, restless legs syndrome (RLS), periodic limb movements during sleep (PLMS), rapid eye movement (REM) sleep behavior disorder (RBD), and intake of betablockers.

PD patients were older than control subjects (PD-wo: 65 ± 10 years, PD-OSAS: 66 ± 8 years; Co-wo: 46 ± 15 years, Co-OSAS: 51 ±13 years). Since age is known to have a major impact on cardiac autonomic function, we aimed for a better matching of age and selected the 62 youngest PD patients and the 62 oldest control subjects for this study. We therefore included 35 PD-wo (mean age: 58 ± 6 years), 27 PD-OSAS (59 ± 6 years), 25 Co-wo (57 ± 12 years), and 37 Co-OSAS (59 ± 8 years).

Clinical assessments. The diagnosis of Parkinson's disease was made according to international diagnostic criteria [13]. Motor symptoms and disease severity were assessed according to the motor subset of the Unified Parkinson's Disease Rating Scale (UPDRS III) in off condition and by the Hoehn & Yahr staging, respectively. Excessive daytime sleepiness (EDS) was diagnosed if the score of the Epworth sleepiness scale was ≥ 10.

Polysomnography. All subjects underwent one full-night polysomnography (Somnologica software). The recordings were performed from 11.00 PM until 7.00 AM using a 16-channel recording system (Embla A10, Embla, Broomfield, CO). Polysomnography included electroencephalographic recording (C3-A2, O2-A1), electro-oculography, chin and bilateral anterior tibialis muscles electromyography, oro-nasal thermistor, nasal flow pressure sensor and measurement of thoracic and abdominal movements (impedance). Oxygen saturation (SaO_2) was continuously determined with a finger oximeter. Scoring of sleep stages and respiratory events was performed visually using standardized criteria [14, 15]. Apnea was defined by a cessation of oro-nasal airflow longer than 10 seconds, and hypopnea by a reduction of oro-nasal airflow by at least 50% lasting more than 10 seconds and accompanied by an arousal or SaO_2 reduction of ≥ 3%. The apnea-hypopnea index (AHI) was calculated by the mean number of apneas and hypopneas per hour. Furthermore, mean SaO_2, time with SaO_2 below 90% (SaO_2 < 90%), and oxygen desaturation-index (ODI) were calculated. OSAS was diagnosed in the presence of AHI ≥ 5/h with predominantly obstructive apneic events.

Heart rate variability analysis. Polysomnography included a two-channel electrocardiogram (ECG) which allowed subsequent analysis of heart rate variability (HRV) by means of a specific HRV-module of the Somnologica software. Heart rate is expressed as average R-R interval in milliseconds, i.e. the mean interval between successive normal QRS complexes. HRV gives information about how the heart rate varies in time. All R-R intervals were processed; artifacts were identified and removed by a specific detection algorithm.

Polysomnographic recordings were divided into continuous 5-minute segments. The most prevailing sleep stage was allocated to every 5-minute segment allowing estimation of mean values per sleep. Calculation of HRV variables in relation to sleep stages is necessary because there is considerable variability of HRV variables between different sleep stages, as shown in healthy subjects [16].

For each 5-minute segment, both time-domain and frequency-domain HRV parameters were computed. The time-domain HRV variables are calculated based on different aspects of the beat-to-beat intervals [16]. For the purpose of this study, the time-domain pattern was estimated by assessing the mean R-R intervals and the standard deviation of normal R-R intervals (SDNN) for each consecutive 5-minute segment. The frequency-domain HRV variables give general information on the power distribution across frequencies. They were obtained by a Fast Fourier spectral analysis of the R-R sequence. The power was calculated for low frequency (LF, 0.04 – 0.15 Hz) and high frequency bands (HF, 0.15 – 0.40). In addition, LF/HF ratio was calculated. Extensive literature exists on the physiological and clinical interpretation of the different power bands [17]. Briefly, the HF power is considered to reflect the parasympathetic (vagal) modulation of the heart rate, whereas the LF power reflects both sympathetic and parasympathetic activity [17]. The LF/HF ratio is believed to be a measure of the sympatho-vagal balance; higher values for this ratio may therefore imply either an increase in sympathetic dominance or a shift towards decreased vagal tone, or both.

Data analysis and statistics. Statistical analyses were performed using SPSS (version 19.0). Group data are described by means and standard deviations (SD). For univariate analysis we used Student's *t* and Mann–Whitney *U* tests for numerical scale variables and χ^2-test for nominal scale variables. Testing of differences in HRV variables and demographic data between multiple groups was performed by the Kruskal-Wallis *H* test. We used

Spearman rho coefficient for correlation analysis between polysomnographic findings and HRV variables. Significance was accepted at $p < 0.05$.

Results

Demographic, clinical and polysomnographic data of the 62 control subjects and the 62 PD patients are given in Table 1. The four groups did not differ in age and sex distribution. Group comparisons did not reveal any differences in the quantitative distribution of sleep stages. In control subjects but not in PD patients, the group with OSAS had higher arousal indices (20.3 ± 20.1 vs. 10.6 ± 7, $p = 0.01$). The prevalence of EDS was significantly higher in Co-OSAS compared to Co-wo ($p = 0.04$) and PD-OSAS ($p = 0.04$), while there were no differences in EDS between PD-OSAS and PD-wo. OSAS severity was similar between PD-OSAS and Co-OSAS for most parameters, but oxygen desaturation was milder in PD-OSAS (Table 2).

In terms of PD symptoms, PD-wo and PD-OSAS had similar prevalences of dyskinesia (36% vs. 33%, $p = 0.54$), wearing-off (33% vs. 30%, $p = 0.51$), hallucinations (17% vs. 29%, $p = 0.28$), RBD (62% vs. 71%, $p = 0.32$), insomnia (56% vs. 52%, $p = 0.48$) and autonomic disturbances (58% vs. 59%, $p = 0.59$). Furthermore, PD-wo and PD-OSAS did not differ in disease duration, disease severity and dopaminergic treatment (Table 1 and 3).

Heart rate variability measures: comparison between Co-wo and PD-wo. In all behavioral stages, the mean R-R interval was lower (faster heart rate) in Co-wo than in PD-wo (wake: 869 ± 115ms vs. 964 ± 182ms, $p = 0.02$; NREM1: 927 ± 136ms vs. 1033 ± 201ms, $p = 0.02$; NREM2: 938 ± 141ms vs. 1035 ± 198ms, $p = 0.03$; SWS: 909 ± 141ms vs. 1036 ± 210ms, $p = 0.009$; REM: 919 ± 123ms vs. 1011 ± 189ms, $p = 0.03$). On the other hand, SDNN and the frequency-domain indices LF, HF and the LF/HF ratio were similar in Co-wo and PD-wo (Figure 1).

Heart rate variability measures: comparison between Co-wo and Co-OSAS. In control subjects, the presence of OSAS was associated with a significant increase in the LF component in both NREM1 and NREM2 sleep and an increase in the LF/HF ratio in NREM1, NREM2 and slow wave sleep (Figure 1). Values for mean R-R and SDNN did not differ between the two groups.

Heart rate variability measures: comparison between Co-OSAS and PD-OSAS. The mean R-R interval and SDNN were similar between Co-OSAS and PD-OSAS. In Co-OSAS, however, the LF component was higher during wakefulness ($p = 0.04$), NREM1 ($p = 0.02$) and REM sleep ($p = 0.02$) and the LF/HF ratio was higher during NREM1 ($p = 0.04$) and REM sleep ($p = 0.008$) (Figure 1).

Heart rate variability measures: comparison between PD-wo and PD-OSAS. The two PD groups did not differ in any of the HRV measures (Figure 1).

Correlates of HRV parameters. In control subjects, AHI significantly correlated with LF and LF/HF ratio in both NREM1 and NREM2 sleep, and AHI was inversely correlated with HF during wakefulness and NREM1 sleep (Table 4). Similar correlations were revealed for ODI. In PD patients, on the other hand, AHI and ODI did not correlate with any of the HRV variables.

Correlates of cortical arousal reaction. In control subjects – but not in PD patients – significant correlations were found between arousal index and HRV measures (Table 4). In addition, while control subjects showed a highly significant correlation between AHI and arousal index (rho = 0.6, $p < 0.001$), this relationship was not found in PD patients (rho = 0.06, $p = 0.64$) (figure 2).

Influence of autonomic disturbances in PD-OSAS. PD-OSAS patients with a history or clinical signs of autonomic disturbances (AD) (56%) – including obstipation (n = 9), urinary incontinence (n = 4), erectile dysfunction (n = 8), orthostatic dysregulation (n = 3) and

sweating disturbances (n = 4) – had significantly lower heart rates in wakefulness, NREM1, NREM2 and REM sleep compared to PD-OSAS without AD (44%) (Figure 3).

Discussion

The main finding of our study is the lack of difference in HRV variables between PD patients with and without OSAS. In control subjects, on the other hand, the presence of OSAS was associated with a significant increase in the low frequency power spectrum during NREM1 and NREM2 sleep and of the LF/HF ratio during NREM1, NREM2 and slow wave sleep. In other words, PD patients lack the normal sympathetic response to OSAS, thus supporting our initial hypothesis. In the same line and again in contrast to controls, parameters of OSAS severity such as AHI, ODI and SaO_2 < 90% did not correlate with any HRV parameters in PD patients. Further novel findings of this study comprise the reduced cortical arousal frequency of PD-OSAS compared to Co-OSAS, and the effect of autonomic disturbances on heart rate in PD-OSAS.

The increase of LF power and LF/HF ratio's in the control group with OSAS indicates enhanced sympathetic drive induced by the repeated apneic events, which is in line with previous studies [1]. To our best knowledge, however, cardiac autonomic response to OSAS has not been assessed yet in PD. Several mechanisms may contribute to the observed impaired cardiac autonomic response to OSAS in PD. First, it is conceivable that the blunted effect of OSAS on cardiac autonomic function reflects the loss of cardiac sympathetic noradrenergic innervation in PD. Evidence of cardiac sympathetic denervation comes mainly from neuroimaging studies, demonstrating decreased myocardial radioactivity after injection of sympathiconeural imaging agents in a majority of PD patients. Using ^{123}I-metaiodobenzylguinidine scanning, cardiac sympathetic denervation was found in early stages of PD, and even in the absence of clinical signs of autonomic failure [18]. In accordance with

these findings, a postmortem pathology study found a marked loss of tyrosine hydroxylase immunoreactivity, a marker for sympathetic nerves, in epicardial nerves or myocardial tissue [12].

Second, autonomic dysfunction in PD is not limited to the heart. According to the study of Braak et al., the neurodegenerative process in many PD patients begins in the medulla oblongata and progresses in an ascending way to involve, already at early stages, various nuclei of the brainstem and also the hypothalamus and other parts of the basal ganglia [19]. The dorsal nucleus of the vagus and the locus coeruleus (LC) are among the first structures to be affected by the disease process. While the former gives rise to parasympathetic vagal neurons, the latter represents the principal source of brain norepinephrine. Besides of its major role in mediating arousal and shifts of behavior, the LC is also believed to be implicated in the central regulation of cardiovascular function [20]. It is therefore conceivable that destruction of pathways of the central autonomic nervous system involved in the regulation of cardiovascular function may additionally contribute to the neurocardiological abnormalities in PD patients with OSAS.

Third, differences in OSAS characteristics between PD patients and control subjects should be taken into consideration. Although our two groups with OSAS did not differ in AHI, ODI, mean apnea duration and mean SaO_2, the PD patients with OSAS maintained a more favorable respiratory profile, as reflected by less pronounced minimal SaO_2 and fewer time spent with $SaO_2 < 90\%$.

An unexpected observation of the present study was the lack of correlation between AHI and arousal index in PD patients – in controls this relationship was highly significant. Several reasons may explain this decrease of arousability in PD. First, sympathetic activation, as measured by heart rate spectral analysis, has been reported to precede visually detected cortical arousals [21]. Thus, an intact sympathetic nervous system may play a relevant role in

conveying the end-apnea effort to a cortical arousal reaction. Second, Onodera et al. studied ventilatory response to hypoxia and perception of dyspnoea in 25 PD patients and found a subnormal hypoxic response accompanied by an impaired perception of dyspnea [22]. Third, multiple components of the central arousal system are known to be damaged in PD, including the noradrenergic LC, the serotonergic dorsal raphe, the cholinergic pedunculopontine nucleus, the hypothalamic hypocretin system and the cholinergic neurons in the basal forebrain [23]. Intriguingly, the assumption of a decreased arousability seems to be inconsistent with the fact that OSAS severity tended to be milder in PD patients, because one would expect more severe apneas under this condition. On the other hand, however, even in healthy subjects about 30% of apneas and hypopneas are not accompanied by cortical arousals [24]. Furthermore, factors such as deeper sleep stage or higher sleep pressure are known to increase the cortical arousal threshold to respiratory events [25]. In other words, cortical arousal must not be regarded as a necessary prerequisite for apnea termination, but rather as a cortical consequence, which depends on the intensity of the inspiratory effort and on the integrity of several components of the central arousal system. Presumably, mechanoreceptor feedback from the respiratory muscles to the medullary respiration center can bring apneas to an end without activation of higher arousal components. Interestingly, this observation could explain the equal prevalence of EDS in PD-wo and PD-OSAS, while the higher arousal index is most likely responsible for the significantly increased sleepiness in Co-OSAS compared to Co-wo.

Interestingly, PD-OSAS patients with autonomic disturbances had significantly slower heart rates during most sleep stages as compared to PD-OSAS without autonomic disturbances. Since sympathetic cardiac denervation has been shown to be more frequent and more pronounced in PD patients with orthostatic hypotension [26], our finding suggests that OSAS in PD may lead to changes of time-domain HRV variables – i.e. decrease of mean R-R

interval – if there is little or no ANS dysfunction. However, since the presence of autonomic disturbances in our patients was detected only by history and clinical examination, this finding has to be replicated in a study, which includes cardiovascular reflex testing.

The clinical implications and the prognostic significance of our observations are not clear at this moment. It is tempting to speculate that the autonomic deficiency might protect PD patients with OSAS to some degree from the typical cardiovascular consequences. In this line, Cochen De Cock et al. did not find an association between OSAS and cardiovascular events in PD patients [27]. In addition, a case-control study of 178 untreated PD patients showed a lower prevalence of vascular risk factors such as diabetes, hypertension, and blood lipid levels than matched non-PD patients [28].

Limitations of this study are its retrospective design and the fact that most PD patients were under dopaminergic treatment at the time of the HRV analysis. Levodopa has been reported to alter cardiovascular reflexes. Thus, we cannot exclude that dopaminergic drugs have influenced the autonomic function in our PD patients. On the other hand, Goldstein et al. found that cardiac sympathetic denervation was not related to levodopa treatment [29]. Likewise, other groups also failed to show any correlation between daily levodopa dose and HRV parameters [30].

In conclusion, our results suggest that the overall pathophysiological profile of OSAS in PD differs from that typically observed in OSAS patients without underlying neurodegenerative disorder. Since the ANS is cardinally involved in mediating the various consequences of OSAS – ranging from immediate effects on cortical arousal reaction to long-term cardiovascular morbidity – the specific disease-modifying impact of ANS dysfunction in PD patients with OSAS warrants further investigation.

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Table 1 Demographic data, clinical characteristics and polysomnographic findings of control subjects (n = 62) and PD patients (n = 62)

Table 2 Comparison of OSAS severity between control subjects and PD patients.

Table 3 Dopaminergic treatment at the moment of polysomnography is similar between PD patients with and without OSAS

Table 4 Spearman correlation coefficients (rho) between HRV variables and various polysomnographic findings in 62 PD patients and 62 control subjects.

Figure 1 Comparison of HRV variables between control subjects with and without OSAS and PD patients with and without OSAS.

Figure 2 While in control subjects the apnea-hypoponea index (AHI) strongly correlated with the arousal index, this association was lacking in PD patients. Similarly, significant correlations between arousal index and LF/HF ratios in NREM1 and NREM2 sleep were found in control subjects but not in PD patients.

Figure 3 PD-OSAS with autonomic disturbances (AD) (n = 15) had a significantly higher mean R-R interval in wake (p = 0.02), NREM1 (p = 0.007), NREM2 (p = 0.03) and REM sleep (p = 0.01) compared to PD-OSAS without clinical signs of AD (n = 12). Conversely, the mean R-R interval did not differ between PD-wo with and without AD.

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For: Parkinsonism and Related Disorders

Heart rate variability in patients with idiopathic Parkinson's disease with and without obstructive sleep apnea syndrome

Philipp O. Valko[1*], MD
Sabrina Hauser[1*], MSc
Esther Werth[1], PhD
Daniel Waldvogel[1], MD
Christian R. Baumann[1], MD

Department of Neurology[1], University Hospital of Zurich, Switzerland

*The first 2 authors contributed equally to this study

Correspondence:

Philipp O. Valko, MD
Department of Neurology
University Hospital of Zurich
Frauenklinikstrasse 26
8091 Zurich, Switzerland
Tel. +41 44 255 55 11
Fax +41 44 255 43 80
E-mail: phvalko@gmx.ch

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Abstract

Background: Obstructive sleep apnea syndrome (OSAS) is associated with repeated apnea-induced sympathetic surges leading to specific alterations of the power spectrum of heart rate variability (HRV). Sympathetic dysfunction evolves early in idiopathic Parkinson's disease (PD), but the consequences on cardiac autonomic response to OSAS have not been studied so far in PD patients.

Methods: Sixty-two patients with PD (35 without OSAS (PD-wo), 27 with OSAS (PD-OSAS)) and 62 age-matched control subjects (25 without OSAS (Co-wo), 37 with OSAS (Co-OSAS)) were included. HRV variables – including mean R-R interval, standard deviation of all normal-to-normal R-R intervals (SDNN), both low frequency (LF) and high frequency (HF) power bands, and the LF/HF ratio – were computed automatically from full-night polysomnography and calculated separately for each sleep stage.

Results: HRV variables were similar in PD-wo and PD-OSAS. In contrast, Co-OSAS showed significantly higher LF power in NREM1 and NREM2 sleep and higher LF/HF ratio in NREM1, NREM2 and slow wave sleep than Co-wo. Similarly, correlations between HRV variables and parameters of OSAS severity were found only in controls but not in PD patients.

Conclusion: Our results suggest that the sympathetic response to OSAS is blunted in PD, giving further clinical evidence of the sympathetic denervation commonly observed in this neurodegenerative disorder.

Introduction

Increased vascular morbidity in patients with obstructive sleep apnea syndrome (OSAS) is believed to be caused by abnormal autonomic cardiovascular regulation [1]. In this line, obstructive sleep-related apnea events are characterized by progressive bradycardia during respiratory effort and abrupt tachycardia after reopening of the airways, which leads to cyclical variations of heart rate [2]. Studies using spectral analysis of heart rate variability (HRV) have shown that OSAS is accompanied by an increase of low frequency power bands, which is believed to reflect sympathetic activity [3]. Likewise, both increased sympathetic nerve activity and high levels of circulating norepinephrine during wakefulness have been observed in patients with OSAS [4-6]. During sleep, obstructive apneas are accompanied by transient vasoconstriction in the limbs, again suggesting apnea-induced sympathetic activation [7]. Finally, there is evidence that alteration of HRV and overactivity of the sympathetic nervous system is reversible during treatment with continuous positive airway pressure [6, 8].

The effects of OSAS on cardiac autonomic function may be altered in patients with neurological conditions affecting the autonomic nervous system (ANS). Earlier studies in patients with familial dysautonomia or pure autonomic failure reported that even severe apneas were not associated with the usual cardiac response, suggesting a decoupling of the heart rate from the respiratory cycle in neurodegenerative disease [9, 10].

In idiopathic Parkinson's disease (PD), there is growing evidence for sympathetic denervation of the heart. Neuroimaging studies using different sympathiconeural imaging agents demonstrated reduced sympathetic innervation of the heart in patients with PD [11, 12]. Considering the important pathophysiological involvement of the ANS in OSAS and its primary impairment in PD, it is surprising that the cardiac autonomic response to OSAS has not yet been studied in PD patients. Therefore, the primary goal of this study was to test the hypothesis whether the normal sympathetic response to OSAS is blunted in PD. In addition,

we aimed at identifying possible consequences of this sympathetic denervation in PD patients with OSAS.

Methods

This retrospective study was conducted at the Department of Neurology of the University Hospital of Zurich, Switzerland.

Subjects. We analyzed the data of 115 consecutive patients with idiopathic Parkinson's disease (PD). All patients were examined in our Movement Disorders outpatient clinic and in our sleep laboratory between January 2005 and June 2010. Fifty-three PD patients were diagnosed with OSAS (PD-OSAS), and 59 had no clinical or polysomnographic signs of OSAS (PD-wo). Three PD patients with apneas of mainly central origin were excluded.

As control groups, we included 80 consecutive patients, who have been diagnosed with OSAS (Co-OSAS), and 53 subjects without OSAS (Co-wo), i.e. without polysomnographic abnormalities. We excluded subjects with cardiovascular disease, cardiac arrhythmia, concomitant diabetes, neurological disorders, additional sleep-wake disorders such as narcolepsy, restless legs syndrome (RLS), periodic limb movements during sleep (PLMS), rapid eye movement (REM) sleep behavior disorder (RBD), and intake of betablockers.

PD patients were older than control subjects (PD-wo: 65 ± 10 years, PD-OSAS: 66 ± 8 years; Co-wo: 46 ± 15 years, Co-OSAS: 51 ±13 years). Since age is known to have a major impact on cardiac autonomic function, we aimed for a better matching of age and selected the 62 youngest PD patients and the 62 oldest control subjects for this study. We therefore included 35 PD-wo (mean age: 58 ± 6 years), 27 PD-OSAS (59 ± 6 years), 25 Co-wo (57 ± 12 years), and 37 Co-OSAS (59 ± 8 years).

Clinical assessments. The diagnosis of Parkinson's disease was made according to international diagnostic criteria [13]. Motor symptoms and disease severity were assessed according to the motor subset of the Unified Parkinson's Disease Rating Scale (UPDRS III) in off condition and by the Hoehn & Yahr staging, respectively. Excessive daytime sleepiness (EDS) was diagnosed if the score of the Epworth sleepiness scale was ≥ 10.

Polysomnography. All subjects underwent one full-night polysomnography (Somnologica software). The recordings were performed from 11.00 PM until 7.00 AM using a 16-channel recording system (Embla A10, Embla, Broomfield, CO). Polysomnography included electroencephalographic recording (C3-A2, O2-A1), electro-oculography, chin and bilateral anterior tibialis muscles electromyography, oro-nasal thermistor, nasal flow pressure sensor and measurement of thoracic and abdominal movements (impedance). Oxygen saturation (SaO_2) was continuously determined with a finger oximeter. Scoring of sleep stages and respiratory events was performed visually using standardized criteria [14, 15]. Apnea was defined by a cessation of oro-nasal airflow longer than 10 seconds, and hypopnea by a reduction of oro-nasal airflow by at least 50% lasting more than 10 seconds and accompanied by an arousal or SaO_2 reduction of ≥ 3%. The apnea-hypopnea index (AHI) was calculated by the mean number of apneas and hypopneas per hour. Furthermore, mean SaO_2, time with SaO_2 below 90% (SaO_2 < 90%), and oxygen desaturation-index (ODI) were calculated. OSAS was diagnosed in the presence of AHI ≥ 5/h with predominantly obstructive apneic events.

Heart rate variability analysis. Polysomnography included a two-channel electrocardiogram (ECG) which allowed subsequent analysis of heart rate variability (HRV) by means of a specific HRV-module of the Somnologica software. Heart rate is expressed as average R-R interval in milliseconds, i.e. the mean interval between successive normal QRS complexes. HRV gives information about how the heart rate varies in time. All R-R intervals were processed; artifacts were identified and removed by a specific detection algorithm.

Polysomnographic recordings were divided into continuous 5-minute segments. The most prevailing sleep stage was allocated to every 5-minute segment allowing estimation of mean values per sleep. Calculation of HRV variables in relation to sleep stages is necessary because there is considerable variability of HRV variables between different sleep stages, as shown in healthy subjects [16].

For each 5-minute segment, both time-domain and frequency-domain HRV parameters were computed. The time-domain HRV variables are calculated based on different aspects of the beat-to-beat intervals [16]. For the purpose of this study, the time-domain pattern was estimated by assessing the mean R-R intervals and the standard deviation of normal R-R intervals (SDNN) for each consecutive 5-minute segment. The frequency-domain HRV variables give general information on the power distribution across frequencies. They were obtained by a Fast Fourier spectral analysis of the R-R sequence. The power was calculated for low frequency (LF, 0.04 – 0.15 Hz) and high frequency bands (HF, 0.15 – 0.40). In addition, LF/HF ratio was calculated. Extensive literature exists on the physiological and clinical interpretation of the different power bands [17]. Briefly, the HF power is considered to reflect the parasympathetic (vagal) modulation of the heart rate, whereas the LF power reflects both sympathetic and parasympathetic activity [17]. The LF/HF ratio is believed to be a measure of the sympatho-vagal balance; higher values for this ratio may therefore imply either an increase in sympathetic dominance or a shift towards decreased vagal tone, or both.

Data analysis and statistics. Statistical analyses were performed using SPSS (version 19.0). Group data are described by means and standard deviations (SD). For univariate analysis we used Student's *t* and Mann–Whitney *U* tests for numerical scale variables and χ^2-test for nominal scale variables. Testing of differences in HRV variables and demographic data between multiple groups was performed by the Kruskal-Wallis *H* test. We used

Spearman rho coefficient for correlation analysis between polysomnographic findings and HRV variables. Significance was accepted at $p < 0.05$.

Results

Demographic, clinical and polysomnographic data of the 62 control subjects and the 62 PD patients are given in Table 1. The four groups did not differ in age and sex distribution. Group comparisons did not reveal any differences in the quantitative distribution of sleep stages. In control subjects but not in PD patients, the group with OSAS had higher arousal indices (20.3 ± 20.1 vs. 10.6 ± 7, $p = 0.01$). The prevalence of EDS was significantly higher in Co-OSAS compared to Co-wo ($p = 0.04$) and PD-OSAS ($p = 0.04$), while there were no differences in EDS between PD-OSAS and PD-wo. OSAS severity was similar between PD-OSAS and Co-OSAS for most parameters, but oxygen desaturation was milder in PD-OSAS (Table 2).

In terms of PD symptoms, PD-wo and PD-OSAS had similar prevalences of dyskinesia (36% vs. 33%, $p = 0.54$), wearing-off (33% vs. 30%, $p = 0.51$), hallucinations (17% vs. 29%, $p = 0.28$), RBD (62% vs. 71%, $p = 0.32$), insomnia (56% vs. 52%, $p = 0.48$) and autonomic disturbances (58% vs. 59%, $p = 0.59$). Furthermore, PD-wo and PD-OSAS did not differ in disease duration, disease severity and dopaminergic treatment (Table 1 and 3).

Heart rate variability measures: comparison between Co-wo and PD-wo. In all behavioral stages, the mean R-R interval was lower (faster heart rate) in Co-wo than in PD-wo (wake: 869 ± 115ms vs. 964 ± 182ms, $p = 0.02$; NREM1: 927 ± 136ms vs. 1033 ± 201ms, $p = 0.02$; NREM2: 938 ± 141ms vs. 1035 ± 198ms, $p = 0.03$; SWS: 909 ± 141ms vs. 1036 ± 210ms, $p = 0.009$; REM: 919 ± 123ms vs. 1011 ± 189ms, $p = 0.03$). On the other hand, SDNN and the frequency-domain indices LF, HF and the LF/HF ratio were similar in Co-wo and PD-wo (Figure 1).

Heart rate variability measures: comparison between Co-wo and Co-OSAS. In control subjects, the presence of OSAS was associated with a significant increase in the LF component in both NREM1 and NREM2 sleep and an increase in the LF/HF ratio in NREM1, NREM2 and slow wave sleep (Figure 1). Values for mean R-R and SDNN did not differ between the two groups.

Heart rate variability measures: comparison between Co-OSAS and PD-OSAS. The mean R-R interval and SDNN were similar between Co-OSAS and PD-OSAS. In Co-OSAS, however, the LF component was higher during wakefulness ($p = 0.04$), NREM1 ($p = 0.02$) and REM sleep ($p = 0.02$) and the LF/HF ratio was higher during NREM1 ($p = 0.04$) and REM sleep ($p = 0.008$) (Figure 1).

Heart rate variability measures: comparison between PD-wo and PD-OSAS. The two PD groups did not differ in any of the HRV measures (Figure 1).

Correlates of HRV parameters. In control subjects, AHI significantly correlated with LF and LF/HF ratio in both NREM1 and NREM2 sleep, and AHI was inversely correlated with HF during wakefulness and NREM1 sleep (Table 4). Similar correlations were revealed for ODI. In PD patients, on the other hand, AHI and ODI did not correlate with any of the HRV variables.

Correlates of cortical arousal reaction. In control subjects – but not in PD patients – significant correlations were found between arousal index and HRV measures (Table 4). In addition, while control subjects showed a highly significant correlation between AHI and arousal index (rho = 0.6, $p < 0.001$), this relationship was not found in PD patients (rho = 0.06, $p = 0.64$) (figure 2).

Influence of autonomic disturbances in PD-OSAS. PD-OSAS patients with a history or clinical signs of autonomic disturbances (AD) (56%) – including obstipation (n = 9), urinary incontinence (n = 4), erectile dysfunction (n = 8), orthostatic dysregulation (n = 3) and

sweating disturbances (n = 4) – had significantly lower heart rates in wakefulness, NREM1, NREM2 and REM sleep compared to PD-OSAS without AD (44%) (Figure 3).

Discussion

The main finding of our study is the lack of difference in HRV variables between PD patients with and without OSAS. In control subjects, on the other hand, the presence of OSAS was associated with a significant increase in the low frequency power spectrum during NREM1 and NREM2 sleep and of the LF/HF ratio during NREM1, NREM2 and slow wave sleep. In other words, PD patients lack the normal sympathetic response to OSAS, thus supporting our initial hypothesis. In the same line and again in contrast to controls, parameters of OSAS severity such as AHI, ODI and SaO_2 < 90% did not correlate with any HRV parameters in PD patients. Further novel findings of this study comprise the reduced cortical arousal frequency of PD-OSAS compared to Co-OSAS, and the effect of autonomic disturbances on heart rate in PD-OSAS.

The increase of LF power and LF/HF ratio's in the control group with OSAS indicates enhanced sympathetic drive induced by the repeated apneic events, which is in line with previous studies [1]. To our best knowledge, however, cardiac autonomic response to OSAS has not been assessed yet in PD. Several mechanisms may contribute to the observed impaired cardiac autonomic response to OSAS in PD. First, it is conceivable that the blunted effect of OSAS on cardiac autonomic function reflects the loss of cardiac sympathetic noradrenergic innervation in PD. Evidence of cardiac sympathetic denervation comes mainly from neuroimaging studies, demonstrating decreased myocardial radioactivity after injection of sympathiconeural imaging agents in a majority of PD patients. Using ^{123}I-metaiodobenzylguinidine scanning, cardiac sympathetic denervation was found in early stages of PD, and even in the absence of clinical signs of autonomic failure [18]. In accordance with

these findings, a postmortem pathology study found a marked loss of tyrosine hydroxylase immunoreactivity, a marker for sympathetic nerves, in epicardial nerves or myocardial tissue [12].

Second, autonomic dysfunction in PD is not limited to the heart. According to the study of Braak et al., the neurodegenerative process in many PD patients begins in the medulla oblongata and progresses in an ascending way to involve, already at early stages, various nuclei of the brainstem and also the hypothalamus and other parts of the basal ganglia [19]. The dorsal nucleus of the vagus and the locus coeruleus (LC) are among the first structures to be affected by the disease process. While the former gives rise to parasympathetic vagal neurons, the latter represents the principal source of brain norepinephrine. Besides of its major role in mediating arousal and shifts of behavior, the LC is also believed to be implicated in the central regulation of cardiovascular function [20]. It is therefore conceivable that destruction of pathways of the central autonomic nervous system involved in the regulation of cardiovascular function may additionally contribute to the neurocardiological abnormalities in PD patients with OSAS.

Third, differences in OSAS characteristics between PD patients and control subjects should be taken into consideration. Although our two groups with OSAS did not differ in AHI, ODI, mean apnea duration and mean SaO_2, the PD patients with OSAS maintained a more favorable respiratory profile, as reflected by less pronounced minimal SaO_2 and fewer time spent with $SaO_2 < 90\%$.

An unexpected observation of the present study was the lack of correlation between AHI and arousal index in PD patients – in controls this relationship was highly significant. Several reasons may explain this decrease of arousability in PD. First, sympathetic activation, as measured by heart rate spectral analysis, has been reported to precede visually detected cortical arousals [21]. Thus, an intact sympathetic nervous system may play a relevant role in

conveying the end-apnea effort to a cortical arousal reaction. Second, Onodera et al. studied ventilatory response to hypoxia and perception of dyspnoea in 25 PD patients and found a subnormal hypoxic response accompanied by an impaired perception of dyspnea [22]. Third, multiple components of the central arousal system are known to be damaged in PD, including the noradrenergic LC, the serotonergic dorsal raphe, the cholinergic pedunculopontine nucleus, the hypothalamic hypocretin system and the cholinergic neurons in the basal forebrain [23]. Intriguingly, the assumption of a decreased arousability seems to be inconsistent with the fact that OSAS severity tended to be milder in PD patients, because one would expect more severe apneas under this condition. On the other hand, however, even in healthy subjects about 30% of apneas and hypopneas are not accompanied by cortical arousals [24]. Furthermore, factors such as deeper sleep stage or higher sleep pressure are known to increase the cortical arousal threshold to respiratory events [25]. In other words, cortical arousal must not be regarded as a necessary prerequisite for apnea termination, but rather as a cortical consequence, which depends on the intensity of the inspiratory effort and on the integrity of several components of the central arousal system. Presumably, mechanoreceptor feedback from the respiratory muscles to the medullary respiration center can bring apneas to an end without activation of higher arousal components. Interestingly, this observation could explain the equal prevalence of EDS in PD-wo and PD-OSAS, while the higher arousal index is most likely responsible for the significantly increased sleepiness in Co-OSAS compared to Co-wo.

Interestingly, PD-OSAS patients with autonomic disturbances had significantly slower heart rates during most sleep stages as compared to PD-OSAS without autonomic disturbances. Since sympathetic cardiac denervation has been shown to be more frequent and more pronounced in PD patients with orthostatic hypotension [26], our finding suggests that OSAS in PD may lead to changes of time-domain HRV variables – i.e. decrease of mean R-R

interval – if there is little or no ANS dysfunction. However, since the presence of autonomic disturbances in our patients was detected only by history and clinical examination, this finding has to be replicated in a study, which includes cardiovascular reflex testing.

The clinical implications and the prognostic significance of our observations are not clear at this moment. It is tempting to speculate that the autonomic deficiency might protect PD patients with OSAS to some degree from the typical cardiovascular consequences. In this line, Cochen De Cock et al. did not find an association between OSAS and cardiovascular events in PD patients [27]. In addition, a case-control study of 178 untreated PD patients showed a lower prevalence of vascular risk factors such as diabetes, hypertension, and blood lipid levels than matched non-PD patients [28].

Limitations of this study are its retrospective design and the fact that most PD patients were under dopaminergic treatment at the time of the HRV analysis. Levodopa has been reported to alter cardiovascular reflexes. Thus, we cannot exclude that dopaminergic drugs have influenced the autonomic function in our PD patients. On the other hand, Goldstein et al. found that cardiac sympathetic denervation was not related to levodopa treatment [29]. Likewise, other groups also failed to show any correlation between daily levodopa dose and HRV parameters [30].

In conclusion, our results suggest that the overall pathophysiological profile of OSAS in PD differs from that typically observed in OSAS patients without underlying neurodegenerative disorder. Since the ANS is cardinally involved in mediating the various consequences of OSAS – ranging from immediate effects on cortical arousal reaction to long-term cardiovascular morbidity – the specific disease-modifying impact of ANS dysfunction in PD patients with OSAS warrants further investigation.

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Table 1 Demographic data, clinical characteristics and polysomnographic findings of control subjects (n = 62) and PD patients (n = 62)

Table 2 Comparison of OSAS severity between control subjects and PD patients.

Table 3 Dopaminergic treatment at the moment of polysomnography is similar between PD patients with and without OSAS

Table 4 Spearman correlation coefficients (rho) between HRV variables and various polysomnographic findings in 62 PD patients and 62 control subjects.

Figure 1 Comparison of HRV variables between control subjects with and without OSAS and PD patients with and without OSAS.

Figure 2 While in control subjects the apnea-hypoponea index (AHI) strongly correlated with the arousal index, this association was lacking in PD patients. Similarly, significant correlations between arousal index and LF/HF ratios in NREM1 and NREM2 sleep were found in control subjects but not in PD patients.

Figure 3 PD-OSAS with autonomic disturbances (AD) (n = 15) had a significantly higher mean R-R interval in wake ($p = 0.02$), NREM1 ($p = 0.007$), NREM2 ($p = 0.03$) and REM sleep ($p = 0.01$) compared to PD-OSAS without clinical signs of AD (n = 12). Conversely, the mean R-R interval did not differ between PD-wo with and without AD.

Table 1

	Co-wo	Co-OSAS	*p*	PD-wo	PD-OSAS	*p*
n	25 (40%)	37 (60%)		35 (56%)	27 (44%)	
Demographic data:						
Male, n	16 (64%)	27 (73%)	NS	19 (54%)	20 (67%)	NS
Age, y	57 ± 12	59 ± 8	NS	58 ± 6	59 ± 6	NS
Clinical characteristics:						
BMI, kg/m^2	26.2 ± 5.3	28.7 ± 4.7	NS	22.6 ± 3.1	28.0 ± 4.9	***<0.001***
ESS	8.0 ± 4.5	11.2 ± 5.6	***0.01***	8.3 ± 4.3	9.7 ± 4.7	NS
EDS (ESS ≥ 10), n	10 (40%)	24 (67%)	***0.04***	13 (39%)	11 (41%)	NS
Disease duration, y				7.2 ± 4.4	8.1 ± 6.9	NS
UPDRS III				22.8 ± 10.9	26.4 ± 13.9	NS
Hoehn & Yahr				2.3 ± 0.8	2.5 ± 0.8	NS
Polysomnographic findings:						
Total sleep time, min	359 ± 64	357 ± 65	NS	330 ± 81	340 ± 67	NS
Sleep latency to NREM2	23.2 ± 16.1	31.8 ± 32.7	NS	26.8 ± 38.1	22.5 ± 17.2	NS
Arousal index, /h	10.5 ± 7.0	20.3 ± 20.1	***0.009***[a]	8.0 ± 4.6	10.6 ± 9.4	NS
Sleep efficiency, %	81.4 ± 11.8	81.6 ± 12.0	NS	76.7 ± 15.3	78.5 ± 12.7	NS
Sleep stage transitions, /h	17.7 ± 5.8	21.1 ± 7.3	***0.047***	19.0 ± 5.9	23.0 ± 21.9	NS
PLMS, /h	0.9 ± 2.3	6.7 ± 9.9	***0.001***	5.5 ± 10.6	17.6 ± 35.9	NS
Wake, %	18.9 ± 11.5	17.8 ± 11.9	NS	22.6 ± 15.2	21.4 ± 12.5	NS
NREM1, %	12.3 ± 5.7	15.8 ± 13.3	NS	12.4 ± 5.4	11.9 ± 8.0	NS
NREM2, %	40.0 ± 9.2	37.1 ± 11.5	NS	37.8 ± 11.2	40.3 ± 10.6	NS
SWS, %	13.5 ± 7.9	16.5 ± 8.5	NS	14.0 ± 9.4	10.7 ± 6.9	NS
REM, %	15.4 ± 6.9	12.3 ± 5.3	NS	13.3 ± 6.0	15.7 ± 8.6	NS

[a] Mann-Whitney *U* test

NS: not significant BMI: Body Mass Index ESS: Epworth Sleepiness Scale EDS: Excessive daytime sleepiness UPDRS III: Unified Parkinson's Disease Rating Scale (Part III=motor score) NREM sleep: Non-Rapid-Eye Movements SWS: Slow wave sleep AHI: Apnea-Hypopnea-Index

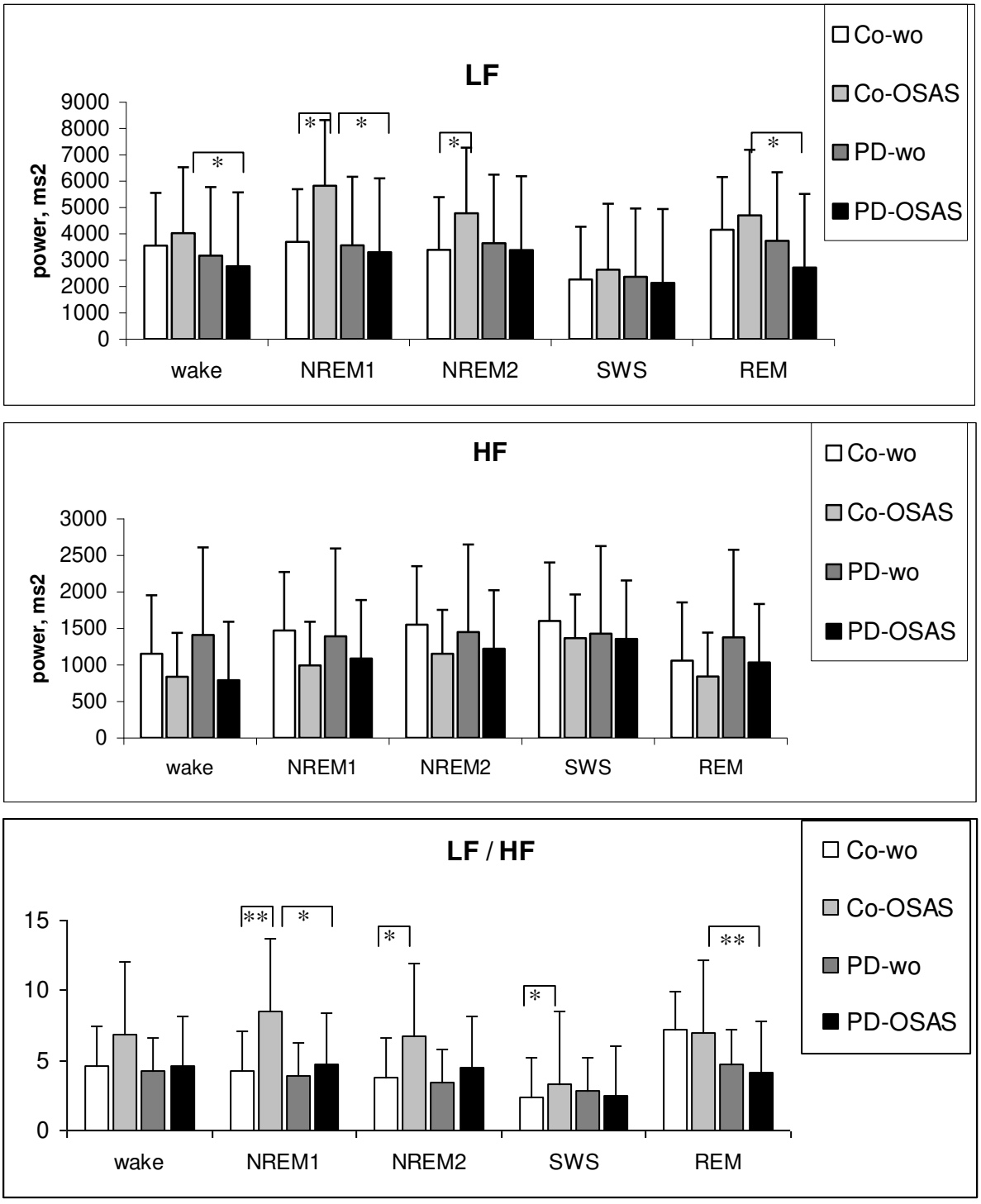
Table 4

	Arousal index		AHI		mean SaO_2		SaO_2<90%		ODI	
	CS	**PD**	**CS**	**PD**	**CS**	**PD**	**CS**	**PD**	**CS**	**PD**
Wake:										
Mean R-R interval	-0.21	0.16	-0.04	-0.03	***0.29****	-0.03	-0.21	0.02	-0.07	-0.05
LF	0.06	0.19	0.09	-0.02	0.19	-0.09	-0.08	0.07	0.07	-0.07
HF	***-0.33****	0.16	***-0.27****	-0.07	0.23	0.12	-0.24	-0.02	***-0.26****	-0.09
LF/HF ratio	***0.25****	-0.03	0.23	0.08	-0.09	-0.18	0.12	0.04	0.23	0.03
NREM1 sleep:										
Mean R-R interval	-0.19	0.11	-0.06	-0.06	***0.38****	0.06	***-0.30****	-0.04	-0.08	-0.09
LF	0.23	0.22	***0.29****	0.07	0.12	-0.03	-0.09	-0.003	0.23	-0.04
HF	***-0.25****	0.18	***-0.30****	-0.11	***0.25****	0.20	-0.22	-0.06	***-0.26****	-0.09
LF/HF ratio	***0.36****	0.03	***0.46*****	0.12	-0.13	-0.24	0.15	0.04	***0.38****	0.05
NREM2 sleep:										
Mean R-R interval	-0.17	0.13	0.01	0.001	***0.34****	-0.01	-0.25	0.01	0.01	-0.04
LF	0.16	0.05	***0.28****	0.07	0.16	-0.19	-0.07	0.09	0.23	-0.03
HF	-0.23	0.14	-0.23	0.05	***0.27****	0.12	***-0.25****	-0.003	-0.19	-0.04
LF/HF ratio	***0.28****	-0.15	***0.39****	-0.02	-0.14	***-0.29****	0.19	0.003	***0.33****	-0.07
Slow wave sleep:										
Mean R-R interval	-0.05	0.15	0.15	-0.03	***0.27****	-0.01	-0.16	-0.007	0.14	-0.08
LF	-0.09	0.02	0.14	0.15	***0.26****	-0.22	-0.22	0.15	0.11	0.01
HF	-0.20	0.21	-0.12	0.18	***0.31****	0.11	-0.19	-0.06	-0.07	0.01
LF/HF ratio	0.10	-0.20	0.24	-0.04	-0.11	***-0.30****	0.05	0.12	0.20	-0.04
REM sleep:										
Mean R-R interval	-0.13	0.08	0.04	0.003	***0.29****	-0.09	-0.18	0.05	0.03	-0.01
LF	-0.14	0.02	-0.01	-0.09	***0.32****	-0.04	***-0.28****	-0.003	-0.06	-0.14
HF	-0.10	0.21	-0.04	0.16	0.10	0.07	-0.03	0.08	0.004	0.12
LF/HF ratio	0.02	-0.21	0.02	-0.25	0.20	-0.21	-0.19	-0.05	-0.04	-0.24

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

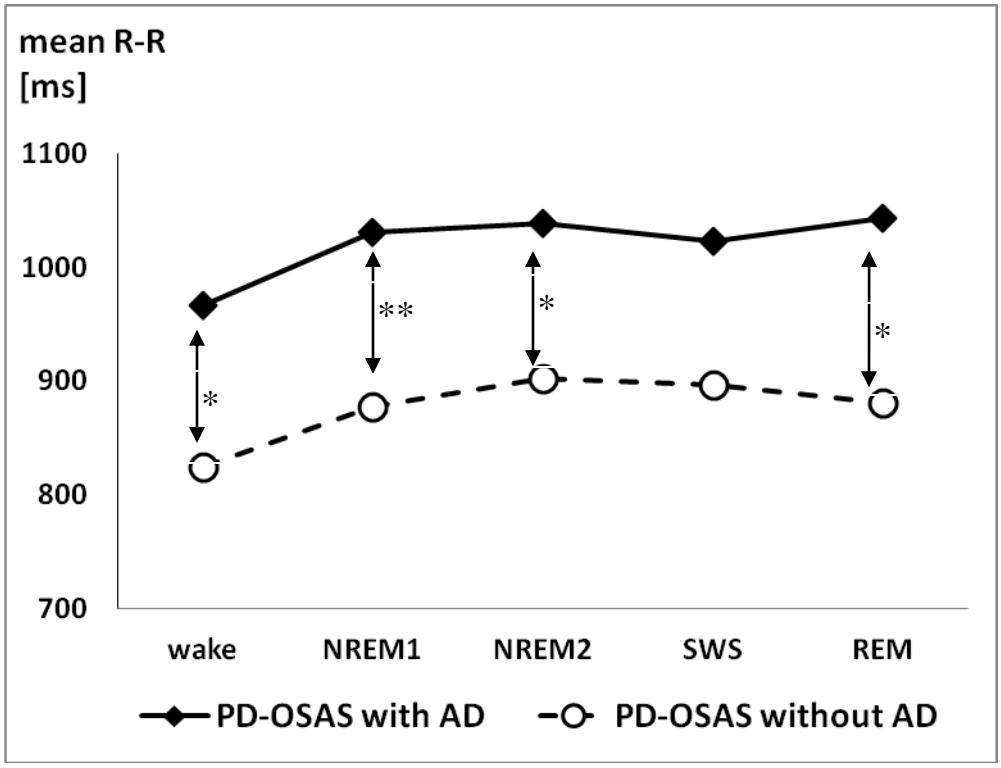
AHI: Apnea-Hypopnea Index CS: control subjects HF: high frequency power LF: low frequency power LF/HF ratio: ratio between low frequency and high frequency power NREM sleep: Non Rapid Eye Movement Sleep ODI: Oxygen Desaturation Index PD: Parkinson's Disease REM: Rapid Eye Movement SaO_2: blood oxygen saturation SaO_2<90%: blood oxygen saturation below 90%

Figure 1



Co-wo: control subjects without OSAS Co-OSAS: control subjects with OSAS PD-wo: PD patients without OSAS PD-OSAS: PD patients with OSAS LF: low frequency power HF: high frequency power LF/HF: ratio between low frequency and high frequency power
* $p < 0.05$, ** $p < 0.01$

Figure 3



* $p < 0.05$ ** $p < 0.01$

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